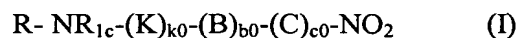


CLAIMS

1. Nitrooxyderivatives or salts thereof having the following general formula (I)



5 wherein

c0 is 0 or 1;

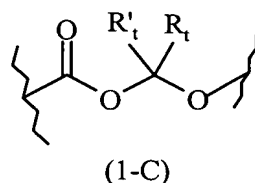
b0 is 0 or 1, with the proviso that c0 and b0 can not be simultaneously 0;

k0 is 0 or 1;

R is the radical of an analgesic drug for chronic pain;

10 R_{1c} being H or straight or branched alkyl with from 1 to 5 carbon atoms;

K is (CO) or the bivalent radical (1C) having the following formula:



wherein the carbonyl group is bound to T_1 ; R_t and R'_t , same or different, are H, C_1 - C_{10} -alkyl, phenyl or benzyl, $-COOR_y$, in which R_y = H, C_1 - C_{10} -alkyl, phenyl, benzyl;

15 B = $-T_B-X_2-T_{BI}-$ wherein

T_B = (CO) or X, in which X = O, S, NH;

with the proviso that:

when $b0 = 1$ and $k0 = 0$, then T_B = (CO);

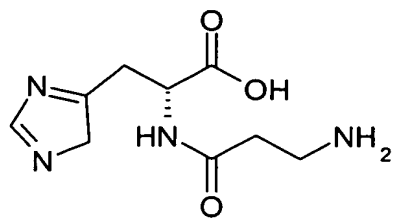
when $b0 = 1$ and $k0 = 1$, being K = (CO), then T_B = X as defined above;

20 T_{BI} = (CO) or (X), wherein X is as defined above;

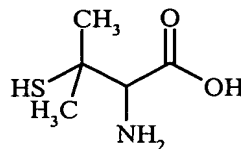
when $c0 = 0$, then T_{BI} = $-O-$;

X_2 is such a bivalent bridging group such as the corresponding precursor of B, having the formula $Z-T_B-X_2-T_{BI}-Z'$ in which Z, Z' are independently H or OH, is selected from the following compounds:

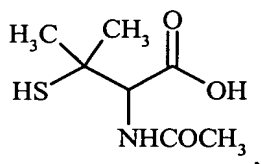
25 - Aminoacids: L-carnosine (CI), penicillamine (CV), N-acetylpenicillamine (CVI), cysteine (CVII), N-acetylcysteine (CVIII):



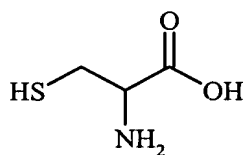
(CI)



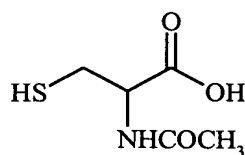
(CV)



(CVI)



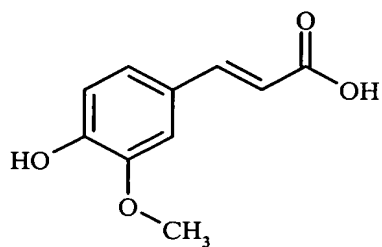
(CVII)



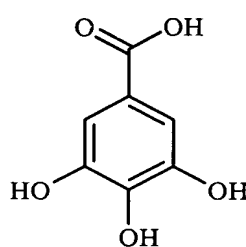
(CVIII)

5

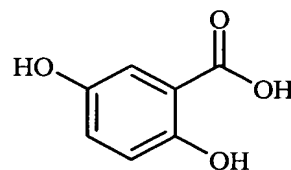
- Hydroxyacids: gallic acid (DI), ferulic acid (DII), gentisic acid (DIII), caffeic acid (DV), hydro caffeic acid (DVI), p-coumaric acid (DVII), vanillic acid (DVIII), syringic acid (DXI):



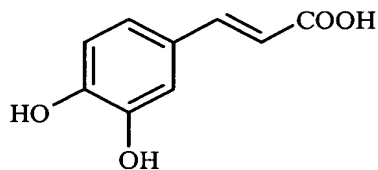
(DII)



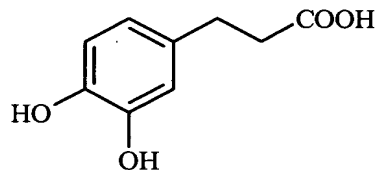
(DI)



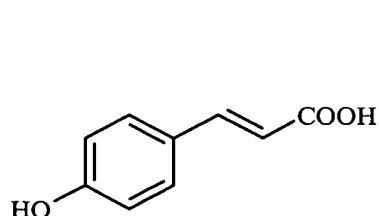
(DIII)



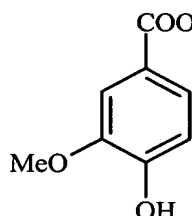
(DV)



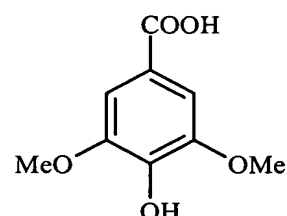
(DVI)



(DVII)



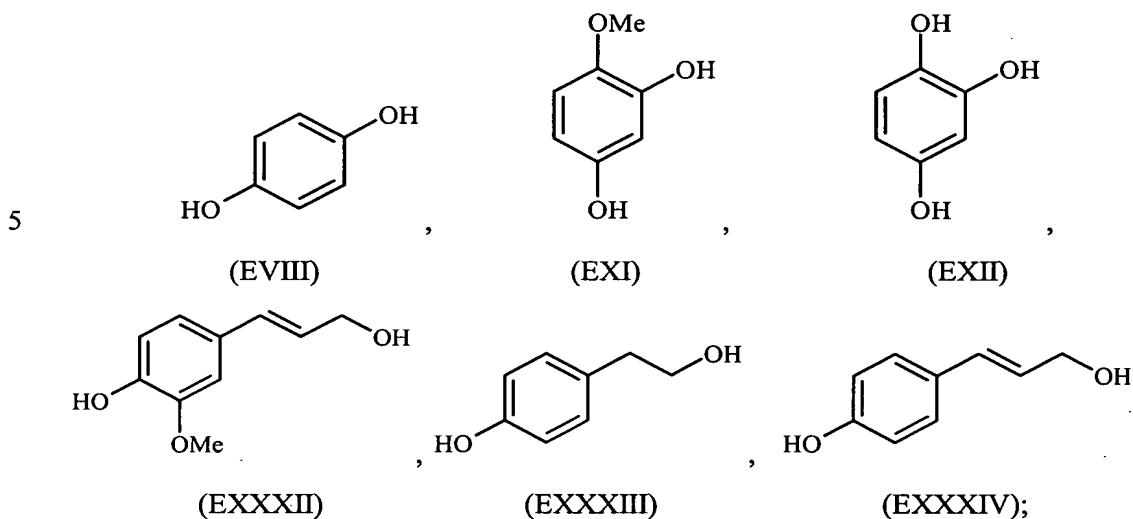
(DVIII)



(DXI)

10

- aromatic polyalcohols: hydroquinone (EVIII), methoxyhydroquinone (EXI), hydroxyhydroquinone (EXII), coniferyl alcohol (EXXXII), 4-hydroxyphenetyl alcohol (EXXXIII), p-coumaric alcohol (EXXXIV):



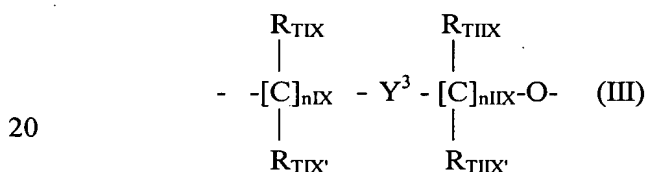
10 C = bivalent radical having the formula $-T_c-Y-$
wherein

$T_c = (CO)$ or X being as defined above;

with the proviso that when $b_0 = 0$ and $k_0 = 1$:

- 15
- $T_c = (CO)$ when $K = (1C)$,
 - $T_c = X$ as defined above when $K = (CO)$; and

Y has one of the following meanings:



wherein:

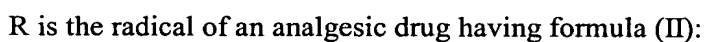
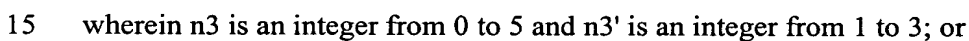
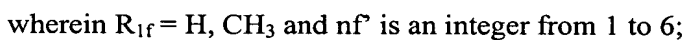
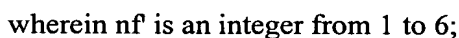
n_{IX} is an integer of from 0 to 5;

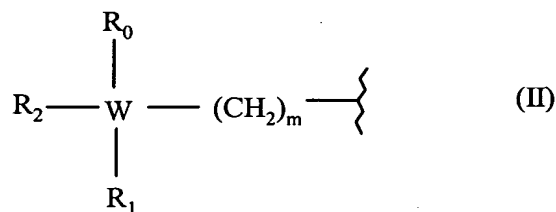
n_{IIX} is an integer of from 1 to 5;

25 R_{TIX} , $R_{TIX'}$, R_{TIIX} , $R_{TIIX'}$, the same or different, are H or straight or branched C_1 - C_4 -alkyl;

or Y may be:

- or one of the following groups:





wherein:

W is a carbon or nitrogen atom;

m is an integer of from 0 to 2;

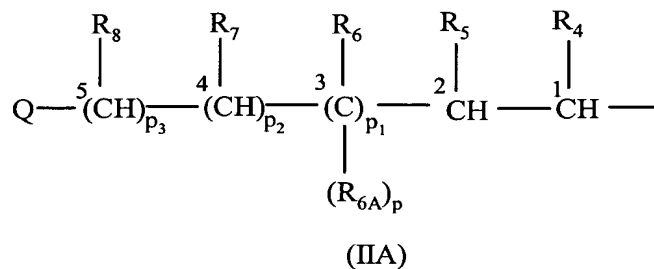
5 $R_0 = H, -(CH_2)_n-COOR_y, R_y$ being as defined above;

n is an integer of from 0 to 2;

$R_1 = H$; when $W = N$, R_1 is the electronic doublet on nitrogen atom (free valence);

R_2 is selected from the following groups:

- phenyl, optionally substituted with a halogen atom or with a group selected from
- 10 $-OCH_3, -CF_3, \text{ nitro}$;
- mono or dihydroxy-substituted benzyl, preferably 3,4-dihydroxybenzyl;
- amidino group: $H_2N(C=NH)-$;
- a radical of formula (IIA), wherein optionally an ethylenic unsaturation may be present between the carbon atoms in position 1 and 2, or 3 and 4 or 4 and 5:



wherein:

p, p_1, p_2 are integers, same or different, and are 0 or 1;

p_3 is an integer of from 0 to 10;

R_4 is hydrogen, straight or branched C_1-C_6 -alkyl, free valence;

20 R_5 may have the following meanings:

- hydrogen,
- straight or branched C_1-C_6 -alkyl,
- C_3-C_6 -cycloalkyl,
- OR_A, R_A having the following meanings:

- straight or branched C₁-C₆-alkyl, optionally substituted with one or more halogen atoms, preferably F,
- phenyl optionally substituted with a halogen atom or with one of the following groups: -OCH₃, -CF₃, nitro;

5 R₆, R_{6A}, R₇, R₈, the same or different, are H, methyl or free valence, with the proviso that when an ethylenic unsaturation is present between C₁ and C₂ in radical of formula (IIA), R₄ and R₅ are free valences able to form the double bond between C₁ and C₂; if the unsaturation is between C₃ and C₄, R₆ and R₇ are free valence able to form the double bond between C₃ and C₄; is the unsaturation
10 is between C₄ and C₅, R₇ and R₈ are free valence able to form the double bond between C₄ and C₅;

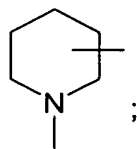
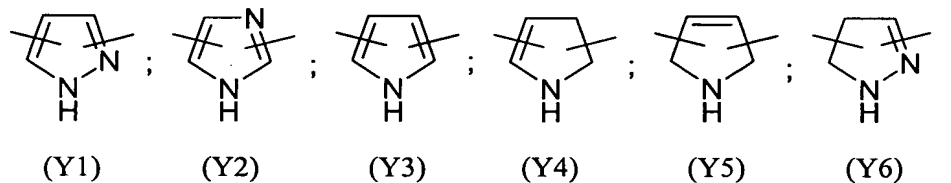
Q is H, OH, OR_B, R_B being benzyl, straight or branched C₁-C₆-alkyl, optionally substituted with one or more halogen atoms, preferably F, phenyl optionally substituted with a halogen atom or with one of the following groups: -OCH₃, -
15 CF₃, nitro; or

Q may have one of the following meanings:

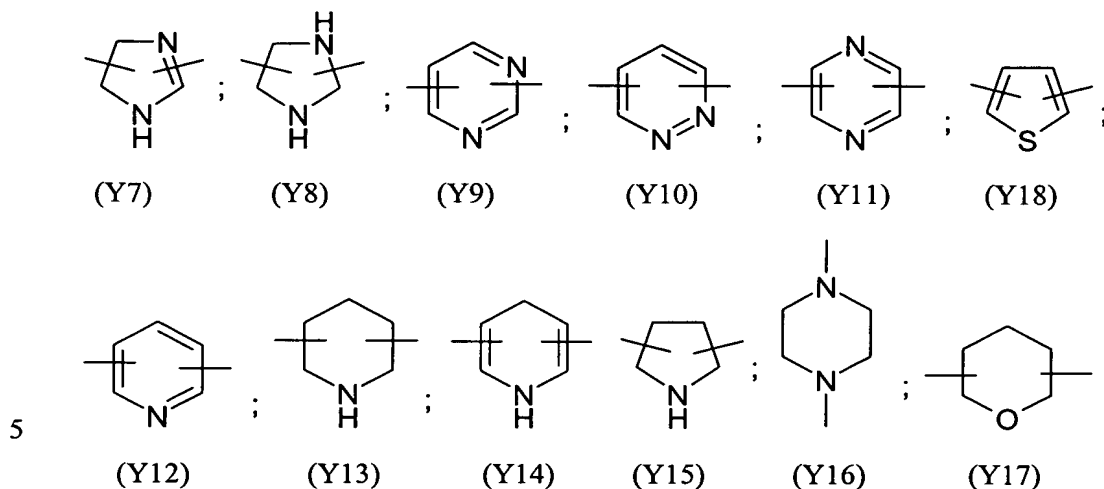
- straight or branched C₁-C₆-alkyl,
- C₃-C₆-cycloalkyl,
- guanidino (H₂NC(=NH)NH-),
- 20 - thioguanidino (H₂NC(=S)NH-).

in formula (II) R₂ with R₁ and with W = C form together a C₄-C₁₀ saturated or unsaturated ring.

2. Compounds according to claim 1, characterized in that Y³ in formula (III) is selected
25 from:



(Y19)



3. Compounds according to claim 1, characterized in that in formula (I):

c0 is 1;

10 b0 is 0 or 1;

k0 is 0 or 1;

R_{1c} = H;

K is (CO) or the bivalent radical (1C) as defined in claim 1;

B = -T_B-X₂-T_{BI}- wherein

15 T_B = (CO) or X, in which X = O, S, NH;

with the proviso that:

when b0 = 1 and k0 = 0, then T_B = (CO);

when b0 = 1 and k0 = 1, being K = (CO), then T_B = X as defined above;

T_{BI} = (CO) or (X), wherein X is as defined above;

20 when c0 = 0, then T_{BI} = -O-;

the precursor of B is N-acetylcysteine or ferulic acid;

C = bivalent radical having the formula -T_c-Y-

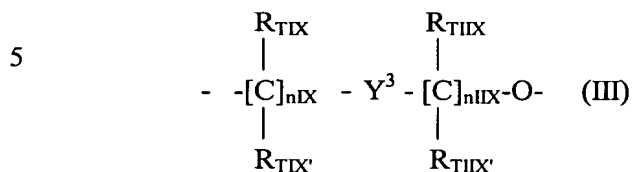
wherein

T_c = (CO) or X being as defined above;

25 with the proviso that when b0 = 0 and k0 = 1:

- T_c = (CO) when K = (1C),

- $T_c = X$ as defined above when $K = (CO)$; and
 Y has one of the following meanings:

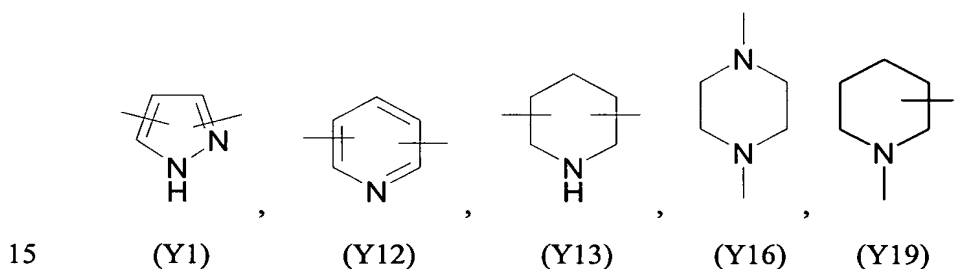


10 wherein:

nIX and $nIIIX$ are 1;

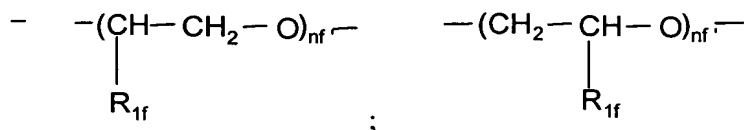
R_{TIX} , $R_{TIX'}$, R_{TIIIX} , $R_{TIIIX'}$ are H;

Y^3 is selected from the following bivalent radicals:

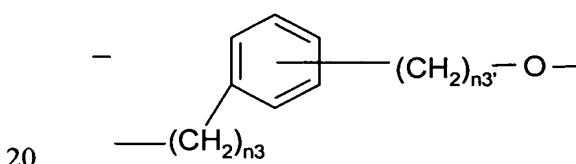


or Y may be:

an alkylenoxy group $-R'O-$ in which R' is straight or branched C_2-C_6 alkyl; or

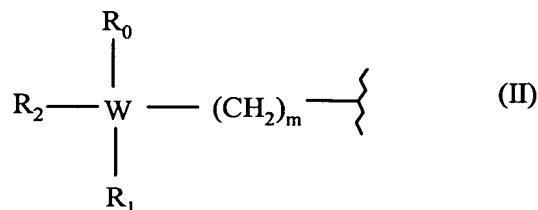


wherein $R_{1f} = H, CH_3$ and nf is an integer from 1 to 4;



wherein $n3$ is an integer from 0 to 3 and $n3'$ is an integer from 1 to 3;

R is the radical of an analgesic drug having formula (II):



wherein:

W is a carbon atom;

m is 0 or 1;

5 $R_0 = H$ or $-(CH_2)_n-COOH$, wherein n is an integer of from 0 to 2;

$R_1 = H$;

R_2 is selected from the following groups:

- 3,4-dihydroxybenzyl; or
- a radical of formula (IIA) as defined in claim 1, wherein:

10 p and p_1 are 0 or 1;

p_2 and p_3 are 0;

R_4 and R_5 are hydrogen, straight or branched C_1 - C_6 -alkyl or free valence;

R_6 and R_{6A} are H;

with the proviso that when an ethylenic unsaturation is present between C_1 and C_2 in

15 radical of formula (IIA), R_4 and R_5 are free valences able to form the double bond between C_1 and C_2 ;

Q is H, CH_3 or

- guanidino ($H_2NC(=NH)NH-$), or
- thioguanidino ($H_2NC(=S)NH-$);

20 in formula (II) R_2 with R_1 and with W form together a C_6 saturated ring.

4. Compounds according to claims 1-3, wherein when in formula (II) $W = C$,

$m = 1$ and $R_0 = -(CH_2)_n-COOR_y$, wherein $n = 1$ and $R_y = H$; R_2 and R_1 with W as defined above form the cyclohexane ring; the drug precursor of R having the

25 formula $R-NH_2$ is known as gabapentin;

when in formula (II) $W = C$, $m = 0$ and R_0 is defined as for gabapentin with $n = 0$; $R_1 = H$; R_2 is the radical of formula (IIA) in which $p = p_1 = 1$, $p_2 = p_3 = 0$, $R_4 = R_5$

= R₆ = R_{6A} = H, Q = H; the drug precursor of R having the formula R-NH₂ is known as norvaline;

when in formula (II) W = C, m = 0 and R₀ if defined as for gabapentin with n = 0; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = 1, p₂ = p₃ = 0, R₄ = R₅ = R₆ = R_{6A} = H, Q is the guanidino group; the drug precursor of R having the formula R-NH₂ is known as arginine;

when in formula (II) W = C, m = 0 and R₀ if defined as for gabapentin with n = 0; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = 1, p₂ = p₃ = 0, R₄ = R₅ = R₆ = R_{6A} = H, Q is the thioguanidino group; the drug precursor of R having the formula R-NH₂ is known as thiocitrulline;

when in formula (II) W = C, m = 1 and R₀ if defined as for gabapentin with n = 1; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = p₂ = p₃ = 0, R₄ = H, R₅ = Q = CH₃; the drug precursor of R having the formula R-NH₂ is known as pregabalin;

when in formula (II) W = C and has (S) configuration, m = 1 and R₀ if defined as for gabapentin with n = 1; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = p₂ = p₃ = 0, R₄ = H, R₅ = Q = CH₃; the drug precursor of R having the formula R-NH₂ is known as (S)3-isobutylGABA;

when in formula (II) W = C and has (S), m = 0; R₀ = R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = 1, p₂ = p₃ = 0, R₄ = R₅ = R₆ = R_{6A} = H, Q is the guanidino group; the drug precursor of R having the formula R-NH₂ is known as agmatine;

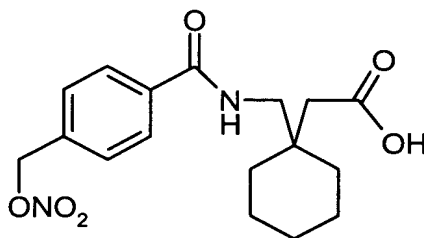
when in formula (II) W = C, m = 0; R₀ if defined as for gabapentin with n = 2; R₁ = H; R₂ is the radical of formula (IIA) in which p = p₁ = p₂ = p₃ = 0, R₄ and R₅ are free valences and between C₁ and C₂ there is an ethylenic unsaturation, Q = H; the drug precursor of R having the formula R-NH₂ is known as vigabatrin;

when in formula (II) W = C, m = 0; R₀ if defined as for gabapentin with n = 0; R₁ = H; R₂ is the 3,4-dihydroxybenzyl radical; the drug precursor of R having the formula R-NH₂ is known as 2-amino-3-(3,4-dihydroxyphenyl)propanoic acid (dopa).

5. Compounds according to claims 1-3, wherein the drug precursors of R in formula (I) are selected from lamotrigine, topiramate, zonisamide, carbamazepine, felbamate, amineptine, amoxapine, demexiptiline, desipramine, nortriptyline, tianeptine.

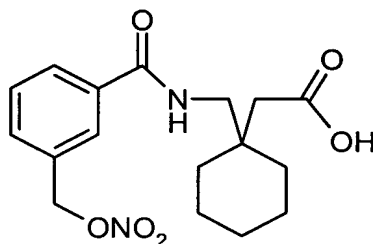
5 6. Compounds according to claims 1, 3 and 4 selected from:

1-[4-(nitrooxymethyl)benzoylaminomethyl]-cyclohexaneacetic acid (XVA),



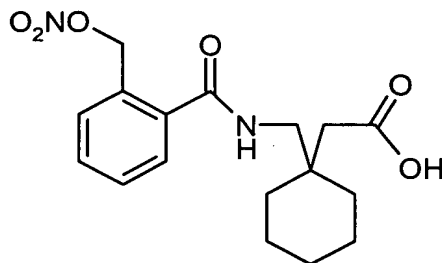
(XVA)

1-[3-(nitrooxymethyl)benzoylaminomethyl]-cyclohexaneacetic acid (XVIA),



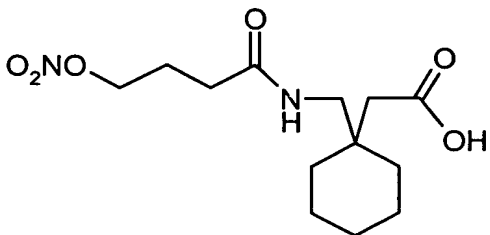
(XVIA)

1-[2-(nitrooxymethyl)benzoylaminomethyl]-cyclohexaneacetic acid (XVIIA),



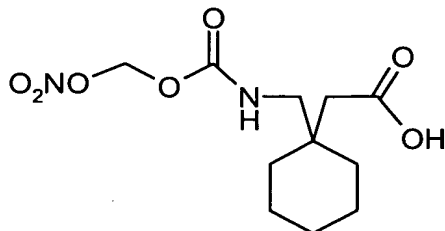
(XVIIA)

15 1-(4-nitrooxybutanoylaminomethyl)-cyclohexaneacetic acid (XVIII),



(XVIII)

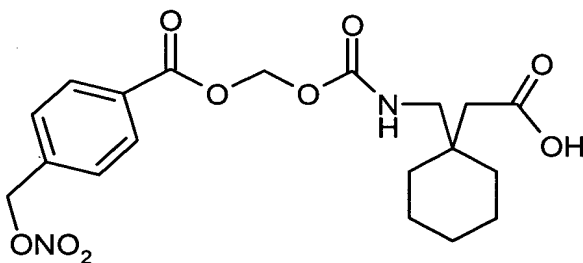
1-(nitrooxymethoxycarbonylaminomethyl)-cyclohexaneacetic acid (XIXA),



(XIXA)

5

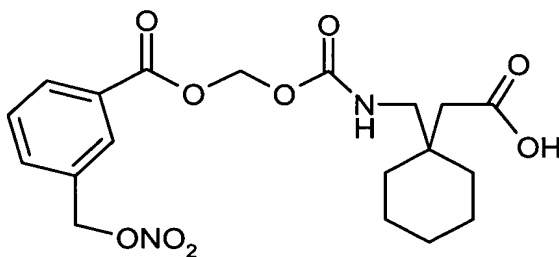
1-{[4-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-cyclohexaneacetic acid (XXA),



(XXA)

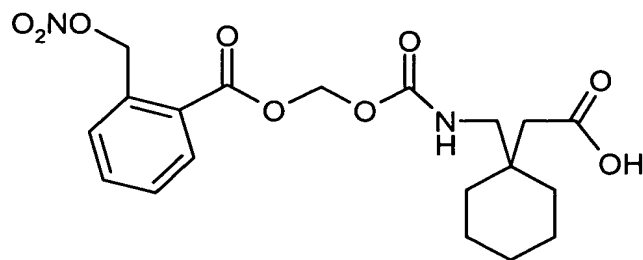
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1-{[3-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-cyclohexaneacetic acid (XXIA),



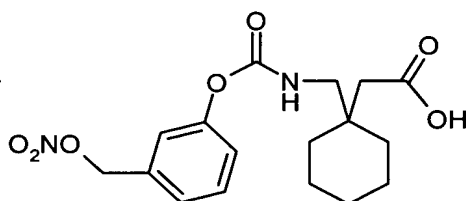
(XXIA)

1-{[2-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-cyclohexaneacetic acid (XXIIA),



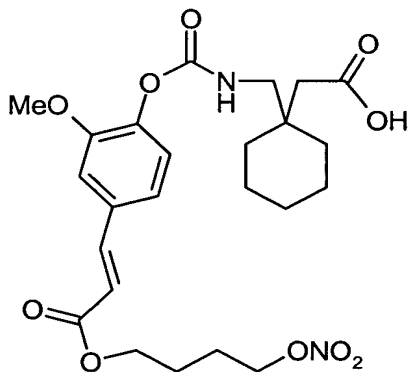
(XXIIA)

5 1-[3-(nitrooxymethyl)phenoxy]methoxycarbonylaminomethyl}-cyclohexaneacetic acid (XXIIIA),



(XXIIIA)

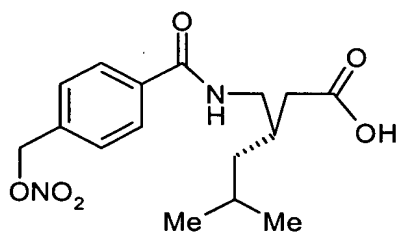
{2-methoxy-4-[(1E)-3-[4-(nitrooxybutoxy)-3-oxa-1-propenyl]phenoxy]-carbonylamino-methyl}-cyclohexaneacetic acid (XXIVA),



(XXIVA)

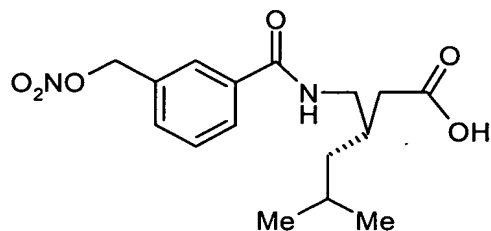
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3-(S)-[4-(nitrooxymethyl)benzoylaminomethyl]-5-methyl-hexanoic acid (XXVA),



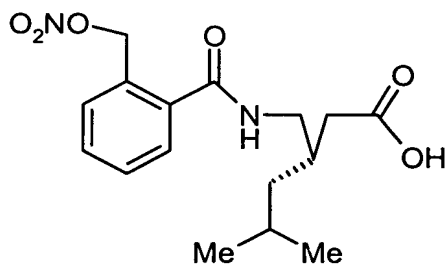
(XXVA)

3-(S)-[3-(nitrooxymethyl)benzoylaminomethyl]-5-methyl-hexanoic acid (XXVIA),



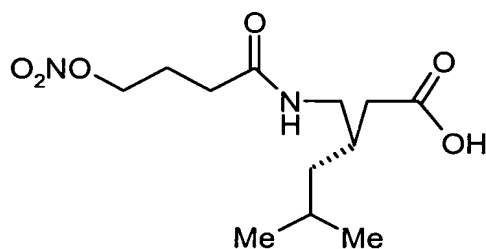
(XXVIA)

5 3(S)-[2-(nitrooxymethyl)benzoylaminomethyl]-5-methyl-hexanoic acid (XXVIIA),



(XXVIIA)

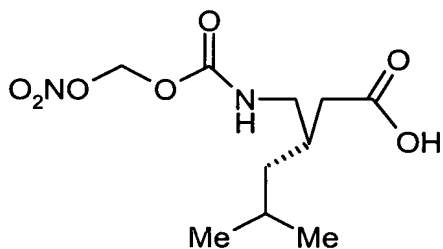
3(S)-[4-(nitrooxybutanoyl)aminomethyl]-5-methyl-hexanoic acid (XXVIII A),



(XXVIII A)

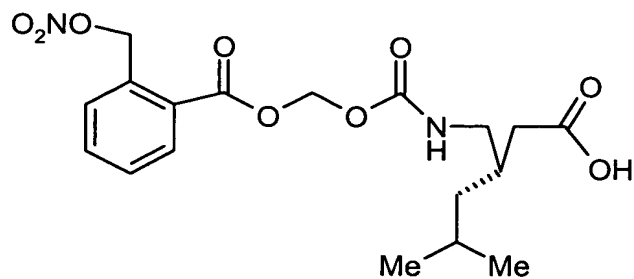
10

3(S)-[4-(nitrooxymethoxycarbonyl)aminomethyl]-5-methyl-hexanoic acid (XXIXA),



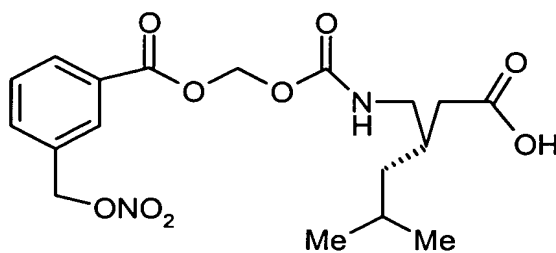
(XXIXA)

15 3(S)-{[2-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-5-methyl-hexanoic acid (XXXA),



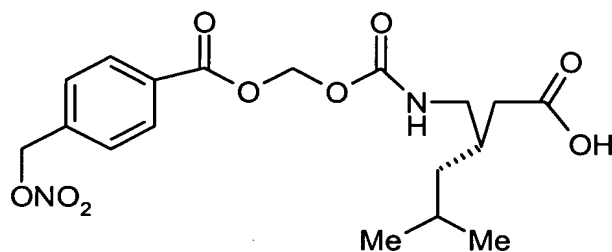
(XXXA)

3(S)-{[3-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl}-5-methyl-hexanoic acid (XXXIA),



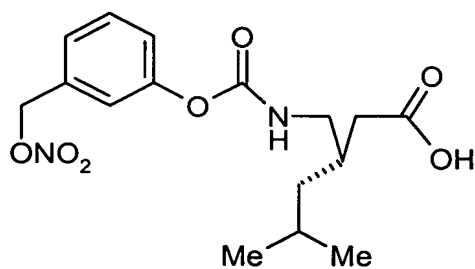
(XXXIA)

3(S)-[4-(nitrooxymethyl)benzoyloxy]methoxycarbonylaminomethyl-5-methyl-hexanoic acid (XXXIIA),



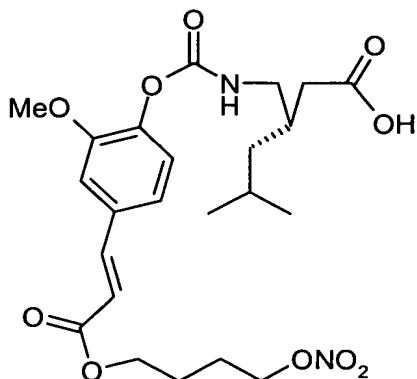
(XXXIIA)

3(S)-[(3-nitrooxymethyl)phenoxy]carbonylaminomethyl-5-methyl-hexanoic acid (XXXIIIA),



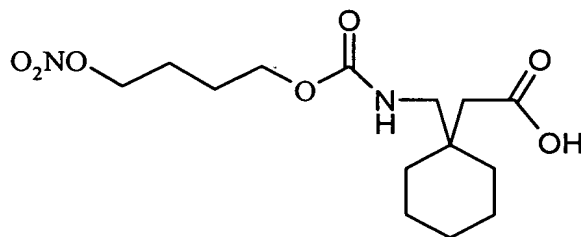
(XXXIIIA)

3(S)-{2-methoxy-4-[(1E)-3-[4-(nitrooxybutoxy)-3-oxa-1-propenylphenoxy]carbonylaminomethyl}-5-methyl-hexanoic acid (XXXIVA),



(XXXIVA)

5 1-[4-(nitrooxybutyloxycarbonyl)aminomethyl]-cyclohexaneacetic acid (XXXVA),



(XXXVA)

7. Compounds according to claims 1-6, in combination with NO-donor compounds.
- 10 8. Compounds according to claim 7, wherein the NO-donors contain in the molecule radicals of the following drugs: aspirin, salicylic acid, ibuprofen, paracetamol, naproxen, diclofenac and flurbiprofen.
- 15 9. Pharmaceutical compositions comprising compounds according to claims 1-8 as active ingredients.
10. Compounds according to claims 1-8 to be employed as a drug.
- 20 11. Use of the compounds according to claims 1-8 for preparing drugs for chronic pain.

12. Use of the compounds according to claim 11, wherein the chronic pain is neurophatic pain.